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TITLE: Genetic Variations in Mitochondria and Prostate Cancer Aggressiveness and Progression in Caucasian and African American Men

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14. ABSTRACT

It has been suggested that some inherited mtDNA variants could have an adverse effect by increasing the generation of reactive oxygen species (ROS). Besides the sequence variations in mtDNA, the mtDNA CNV might also affect cancer risk by disturbing crosstalk between the mitochondria and the nucleus, and consequently altering nuclear DNA stability. Variability in the mtDNA (sequence and copy number) might be extremely relevant to prostate cancer because oxidative stress has been suggested to play a significant role in prostate cancer carcinogenesis. Even more intriguingly, the geographic and racial polymorphisms of mtDNA might have implications in the racial disparity of prostate cancer because African Americans are at a disproportionately higher risk for many oxidative stress–related medical conditions, including prostate cancer. In this current proposal, we plan to utilize the valuable biospecimens and data collected through North Carolina-Louisiana Prostate Cancer Project (PCaP) to comprehensively study the associations between mtDNA polymorphisms/haplogroups and prostate cancer tumor characteristics at baseline and progression in both CA and AA men. Our hypothesis is that genetic variations (sequence and copy number) in mtDNA are associated with prostate cancer aggressiveness at diagnosis and prostate cancer progression. So far, we have completed genotyping analyses for 75 genetic polymorphisms in all study subjects for Aim 1. In Aim 2, we have completed CNV analyses in about 500 study subjects. We have not started Aim 3 yet.

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Introduction

The mitochondrial genome is highly polymorphic among individuals and exhibits significant geographic and racial differences. It has been suggested that some inherited mtDNA variants could have an adverse effect by increasing the generation of reactive oxygen species (ROS). Besides the sequence variations in mtDNA, the mtDNA CNV might also affect cancer risk by disturbing crosstalk between the mitochondria and the nucleus, and consequently altering nuclear DNA stability. It has been proposed that the copy number of mitochondria per cell reflects the gene-environmental interactions between unknown hereditary factors and the levels of oxidative stress. However, whether the mtDNA CNV could be a predictor of human cancer risk and progression or not remains to be determined. Variability in the mtDNA (sequence and copy number) might be extremely relevant to prostate cancer because oxidative stress has been suggested to play a significant role in prostate cancer carcinogenesis. Considerable effort has been made to discover genetic variation that influences susceptibility to prostate cancer development and progression. However, few have been identified to date. The dilemma might be due to the fact that some of the susceptibility alleles might not reside in nuclear DNA, but in mtDNA. Even more intriguingly, the geographic and racial polymorphisms of mtDNA might have implications in the racial disparity of prostate cancer because African Americans are at a disproportionately higher risk for many oxidative stress–related medical conditions, including prostate cancer. Therefore, the investigation into the role of genetic variation in the mitochondria as a susceptibility factor for prostate cancer could have significant impact on cancer research. In this current proposal, we plan to utilize the valuable biospecimens and data collected through North Carolina-Louisiana Prostate Cancer Project (PCaP) to comprehensively study the associations between mtDNA polymorphisms/haplogroups and prostate cancer tumor characteristics at baseline and progression in both CA and AA men. Our hypothesis is that genetic variations (sequence and copy number) in mtDNA are associated with prostate cancer aggressiveness at diagnosis and prostate cancer progression. The proposed study will represent the first study to address the roles of mtDNA variations in prostate cancer aggressiveness and progression as well as racial difference.

Body

Study subjects, biospecimens, and data: We experienced a 8-month delay for getting biospecimens and data from PCaP biobank hosted at UNC. There are two reasons for the delay. At first, it took 4 months to complete the material transfer agreement between M.D. Anderson Cancer Center and UNC. At second, because of the personnel changes, PCaP biobank couldn't process our request for DNA samples and data on time. Until the end of May, we finally obtained the DNA samples and data.

Specific aim 1: we will *evaluate whether genetic variations in mtDNA are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men*. To achieve this goal, we will estimate the frequencies of mtDNA genetic variants in 2,264 prostate cancer cases (1,139 CAs and 1,125 AAs) from PCaP.

The genotypes and haplogroups will be correlated with prostate cancer characteristics at diagnosis for all men. The sub-set of North Carolina PCaP men have been followed for on average 5 years. Five-year biochemical failure (rise in PSA levels) will be the index of prostate cancer 'progression' in this study. We will evaluate the genotypes and haplogroups in relation to the 5-year biochemical failure status in the patients who have at least five years of follow-up. In further analyses, we will assess whether the associations are different between AA and CA men while adjusting for confounding. So far, among 175 proposed genetic polymorphisms, we have already completed the genotyping analysis for 75 polymorphisms for all study subjects. The rest of the genotyping analysis is still ongoing. Once we complete all of them, we will begin the data analysis.

Specific aim 2: we will *evaluate whether mtNDA CNVs are associated with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in CA and AA men, and whether the associations are different between CA and AA men.* To achieve this goal, we will quantify the ratio of mtDNA to nuclear DNA, which is an index for the copy number of mitochondria per cell, in 2,264 prostate cancer cases (1,139 CAs and 1,125 AAs) from PCaP. The mtDNA copy number will be correlated with prostate cancer characteristics at diagnosis (aggressiveness status, PSA, stage and grade) and the 5-year biochemical failure status in the patients who have at least five years of follow-up. In further analyses, we will assess whether the associations are different between AA and CA men while adjusting for confounding. So far, we have completed the CNV analysis for 500 study subjects. The rest of the CNV analysis is still ongoing. Once we complete all of them, we will begin the data analysis.

Specific aim 3: we will *explore and perform whole mitochondrial DNA sequencing to identify novel genetic variants in AA and CA prostate cancer patients.* A subset of the study population from PCaP will be selected for sequencing analysis. There will be 25 AA cases with high aggressive prostate tumors, 25 AA cases with low aggressive prostate tumors, 25 CA cases with high aggressive prostate tumors, and 25 CA cases with low aggressive prostate tumors. Any identified novel genetic variant with a minor allele frequency of at least 5% will be further evaluated in terms of their relationship with aggressive tumor characteristics of prostate cancer at diagnosis and progression of prostate cancer in the full cohort of CA and AA PCaP men. So far, we haven't started on this project yet.

Overall, although we experienced the delay at start, we are very confident that we can catch up and still complete the proposed analyses on time. No major delay is forecasted for second and third year.

Key Research Accomplishments

1. We have obtained the biospecimens and data from 2,264 prostate cancer cases (1,139 CAs and 1,125 AAs) from PCaP.

2. Among 175 proposed genetic polymorphisms, we have already completed the genotyping analysis for 75 polymorphisms for all study subjects.

3. We have completed the CNV analysis for 500 study subjects.

Reportable outcomes

Because the study is still ongoing, at this point, we don't have any manuscript in preparation. But, we expect to begin to prepare two manuscripts pretty soon.

Conclusion

We experienced the delay at start. However, once we obtained the biospecimens, the study has run smoothly so far. We don't expect any delay.